A POTPOURRI OF ORAL MEDICINE AND PATHOLOGY

or

I’ve Always Wondered About That Stuff

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Outline

- Immunologically-mediated diseases
  - Recurrent aphthous ulcers
  - Lichen planus
- Infectious diseases
  - Human herpes virus, Type 1
  - Oral candidiasis
  - Human papilloma virus
- Oral cancer
Aphthous Ulcers

Etiology and Epidemiology

- Immune dysfunction
- Microbial cross-reactivity
- Nutritional deficiency
- Hormonal imbalance
- "Stress"
- Most common oral ulcer
  - 50% of adults in USA affected

Clinical Features

- Never preceded by vesicles
- Only affect non-keratinized mucosa
  - NOT hard palate
  - NOT attached gingiva
- Multiple clinical forms
Minor Aphthous Ulcers
- Most common form
- Small (<1.0 cm)
- Shallow ulcer
- Pseudomembranous covering
- Erythematous halo
- Persist for 7 – 10 days
- Heal without scarring

Major Aphthous Ulcers
- More severe form
- Larger (>1.0 cm)
- Deeper (into muscle)
- Persist for 2-6 weeks
- Heal with scarring

Herpetiform Aphthous Ulcers
- NOT due to infectious agent
- Cluster of multiple small aphthae
- Extremely painful
- Soft palate
- Alveolar mucosa
Differential Diagnosis
- Other viral infections
- Traumatic ulcers
- Pemphigus vulgaris
- Cicatricial pemphigoid
- Crohn’s disease
- Other systemic disease

Diagnosis
- History
  - Clinical signs and symptoms
  - Biopsy ONLY to rule out other entities

Treatment
- OTC medications
- Immunosuppressives
- Occlusive dressings
- Chemical cautery
- Ablation
- Topical antimicrobials
- Thalidomide
Lynch’s Law
When in doubt, treat conservatively

Lynch’s Corollary
When something works, keep using it until it doesn’t

Lynch’s Paradox
What works for me may not work for you and vice versa
Occlusion

Chemical Cautery

Herbals and Lysine
Sodium Lauryl Sulfate

- Extracted from palm oil and coconut oil
- Anionic surfactant (detergent)
  - Makes toothpastes "foamy"
- At higher concentrations, also an effective biocide, pesticide and shark repellent (!)
- Decreases effectiveness of topical F-
- Triggers oral aphthae in some patients

Topical Anesthetics

Coating Agents
Non-steroidal Anti-inflammatory Agents

Cortisone
- Described in 1935
- Converted to hydrocortisone in the liver (active form)

Topical Corticosteroid Potency
- Class I (superpotent) – clobetasol
- Class II (high potency) – fluocinonide
- Class V (moderate potency) – triamcinolone
- Class VII (low potency) – hydrocortisone
Kenalog in Orabase

- Only FDA-approved topical corticosteroid for oral mucosal use
- Least potent topical corticosteroid used in dentistry

High/Super Potency Topical Corticosteroids

Swish and Spit
Swish and Swallow
Injectable Kenalog

- Good for solitary major aphthae that do not respond to topical therapy

Systemic Corticosteroids

<table>
<thead>
<tr>
<th>CORTICOSTEROID</th>
<th>EQUIVALENT DOSE (mg)</th>
<th>GLUCOCORTICOID POTENCY</th>
<th>BIOLOGIC HALF-LIFE (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHORT-ACTING</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisone</td>
<td>25</td>
<td>0.8</td>
<td>8-12</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>20</td>
<td>1</td>
<td>8-12</td>
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<tr>
<td>INTERMEDIATE-ACTING</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>5</td>
<td>4</td>
<td>24-36</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5</td>
<td>4</td>
<td>24-36</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>4</td>
<td>5</td>
<td>24-36</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>4</td>
<td>5</td>
<td>24-36</td>
</tr>
<tr>
<td>LONG-ACTING</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.75</td>
<td>20-30</td>
<td>36-54</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>0.6 – 0.75</td>
<td>20-30</td>
<td>36-54</td>
</tr>
</tbody>
</table>
Daily Cortisol Production
- 20-30 mg (equivalent to 5 - 7.5 mg prednisone)
- 50-75 mg minor stress production
- 300 mg maximum stress production

Excess Glucocorticoid Production (Cushing Disease)

Prognosis
- Excellent
- Variable recurrences
Etiology

- T-cell mediated autoimmune damage to basal keratinocytes that express altered self-antigens on their surface
- Multiple potential triggers
  - Hepatitis C; HBV immunization
  - Primary biliary cirrhosis
  - Other viruses – HHV-6, HHV-7
  - Contact allergens
  - Drugs

Epidemiology

- Middle age
- Females >> males
- Exacerbated by “stress”
Clinical Features (Skin)
- Purple, polygonal, pruritic papules
- Peripheral Wickham’s striae
- Flexor wrists, dorsal hands, ankles, feet, thighs, glans penis
- >65% with oral lesions

Clinical Features (Nails)
- 10% of patients
- May be the only feature in children
- Lateral thinning
- Longitudinal ridging and splitting
- Onycholysis
- Red lunula
- Pterygium formation

Clinical Features (Genital)
Clinical Features (Esophagus)

Clinical Features (Oral)
- Widespread involvement
  - 75% buccal mucosa and tongue
  - 20% labial mucosa and gingiva
  - <5% palate and floor of mouth
  - <35% with skin lesions
- Multiple clinical forms
  - Reticular/plaque forms - asymptomatic
  - Erosive/atrophic/bullous forms - symptomatic

Differential Diagnosis
- Leukoplakia
- Lupus erythematosus
- Aphthous ulcers
- Pemphigus vulgaris
- Cicatricial pemphigoid
- Erythema multiforme
**Diagnosis**
- Biopsy is mandatory
- Routine histopathology
- Direct immunofluorescence
  - BMZ fibrinogen to rule out LE

**Treatment**
- No treatment for asymptomatic cases
- Corticosteroids
- Antimetabolites
- Dapsone
- Cyclosporine
- Occlusive dressings

**Calcineurin Inhibitors**
Prognosis

- Good prognosis
- Moderate morbidity (symptomatic forms)
- Exacerbations and remissions
- (?) premalignant potential
  - <2%
  - Lichenoid dysplasia

- Excellent
- Variable recurrences
Recurrent Herpes Simplex

Etiology and Epidemiology
- Human Herpes Virus 1 (HHV-1)
- #2 most common viral disease
- Majority of individuals in USA exposed
- 50% of individuals give history of contact
- 15% asymptomatic shedders

Clinical Features
- Prodrome
  - Burning
  - Itching
  - Tingling
- Recurrences due to stress
  - Trauma
  - Emotion
  - Endocrine
Clinical Features

- Herpetiform cluster of vesicles
  - Vermilion border
  - Attached gingiva
  - Hard palate
- Infectious for 5-7 days
- Heal in 14 days

Differential Diagnosis

- Impetigo
  - Recurrent aphthous ulcers
  - Traumatic ulcers
  - Other viral stomatitis

Diagnosis

- History
- Clinical signs and symptoms
- Serology
- Viral culture
- Tzanck test
Treatment
- Non-prescription topical antiviral drugs
  - Abreva®
- Prescription topical antiviral drugs
  - Denavir®
  - Zovirax®
- Prescription systemic antiviral drugs
  - Zovirax®
  - Famvir®
  - Valtrex®

Antivirals

Topical Antivirals
Systemic Antivirals

Treatment
- OTC remedies
- Iontophoresis
- Do not use corticosteroids

Lysine
Candidiasis

Etiology and Epidemiology
- *Candida albicans*
- Most common fungal infection
- 35% of healthy adults
- 90% of denture wearers
- Females > males

Predisposing Factors
- Antibiotics
- Xerostomia
- Immunodeficiency
  - Infancy
  - Antimetabolites
  - Acquired
- Malnutrition
- Endocrine dysfunction
  - Diabetes mellitus
  - Pregnancy
  - Oral contraceptives
  - Corticosteroids
Pseudomembranous Candidiasis

- Infants and debilitated adults
- White, non-adherent plaques
- Erythematous base
- Stomatopyrosis
- Stomatodynia

Differential Diagnosis

- Chemical burn
- Allergy
- Hypersensitivity
- Mucous patch
- Morsicatio buccarum / lingualis / labialis

Erythematous candidiasis

- Most common form
- Diffuse erythema
- Variable symptoms
- “denture sore mouth”
  - Limited to denture bearing mucosa
  - Frequently painless
Perlèche

- Angular cheilitis
- Moist, macerated, cracked
- Variable symptoms
- (?) role of decreased vertical dimension
- (?) role of vitamin B complex deficiency

Median Rhomboid Glossitis

- Not a congenital defect
- Posterior dorsal tongue
- Red, depapillated area
- Frequently painless
- Unknown significance

Differential Diagnosis

- Erosive / atrophic lichen planus
- Chemical burn
- Allergy / hypersensitivity
- Impetigo
- Geographic tongue
Diagnosis

- Smear
- Culture
- Biopsy
- Latex agglutination
- Therapeutic diagnosis

Treatment

- Topical antifungals
  - Systemic antifungals
  - Topical antimicrobials

Topical Antifungals

- Nystatin (Mycostatin®)
  - Oral suspension
  - Pastilles
  - Vaginal suppositories
  - Cremes and ointments

- Clotrimazole (Mycelex®)
  - Troche
  - Cremes and ointments
Systemic Antifungals
- Ketoconazole (Nizoral®)
- Fluconazole (Diflucan®)
- Itraconazole (Sporanox®)

Topical antimicrobials
- Gentian violet
- Chlorhexidine
  - Periex
  - Periogard
  - Paroex

Prognosis
- Excellent prognosis
- Frequent recurrences
- Treat predisposing factors
**Human Papillomavirus**

- Epitheliotropic DNA virus
- >120 HPVs
  - Common warts – HPV 2, 7
  - Plantar warts – HPV 1, 2, 4, 63
  - Flat warts – HPV 3, 8, 10
  - Anogenital warts – HPV 6, 11, 42, 44
  - Anal lesions – HPV 6, 16, 18, 31, 53, 58

**Human Papillomavirus**

>120 HPVs (continued)

- Genital cancers –
  - HPV 16, 18, 31, 45 (highest risk)
  - HPV 33, 35, 39, 51, 52, 56, 58, 59 (high risk)
  - HPV 26, 53, 66, 68, 73, 82 (? high risk)
- F.E.H. (Heck’s disease) – HPV 13, 32
- Oral papillomas – 6, 7, 11, 16, 32
- Laryngeal papillomatosis – 6, 11
- Oropharyngeal cancer – 16, 18

**HPV Epidemiology**

- 20 million Americans are HPV+
- 6 million new cases annually
- 50% of sexually active adults will be HPV+ in their lifetime
- 33,000 HPV-related malignancies annually
- 12,000 HPV-related oral malignancies annually (36.4 percent of cases)
HPV Epidemiology

- 560,000 new cancers world-wide (5.2%)
- HPV 16 and 18 associated with 99.7% of all cervical cancers
- HPV 16, 18, 31, 35 are “high risk” for genital cancers
- HPV 16 associated with oropharyngeal cancer

HPV Prevalence

- Peaks with sexual activity
  - 14-19 year olds – 24.5% HPV+
  - 20-24 year olds – 44.8% HPV+
  - 25-29 year olds – 27.4% HPV+
  - 30-39 year olds – 27.5% HPV+
  - 40-49 year olds – 25.2% HPV+
  - 50-59 year olds – 19.6% HPV+
  - 14-59 year olds – 26.8% HPV+ (average)

HPV Transmission

- Perinatal transmission rare
  - HPV 6 and 11 -> respiratory papillomatosis
- Venereal transmission
  - Penile-vaginal
  - Penile-anal (17-31X in gay/bisexual men)
  - Oral
HPV Transmission
- A female college freshman who has one sex partner per year for four years has >85% probability of graduating with an HPV infection
- Hands
  - Self-inoculation of hands from genitalia and vice versa
  - Cross-inoculation of hands from genitalia and vice versa
  - No role for non-sexual hand contact

HPV Transmission
- Shared objects
  - may transmit HPV
- Blood
  - may transmit HPV
- Environmental surfaces, e.g., floor (plantar warts)

HPV Transmission
- Infection through micro-abrasion or other trauma
- Limited to basal cells of stratified squamous epithelium
- Released when epithelial cells desquamate
- Survive for months on environmental surfaces
HPV Infection

- Most infections cleared by the immune system
  - 97-100% of high-risk HPV infections cleared in 18 months
- Persistent infection may lead to cancer

HPV-related Cancers

<table>
<thead>
<tr>
<th>SITE</th>
<th>ANNUAL</th>
<th>HPV</th>
<th>HPV 16/18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix</td>
<td>12,000</td>
<td>11,500</td>
<td>9,100</td>
</tr>
<tr>
<td>Vulvar</td>
<td>3,100</td>
<td>1,600</td>
<td>1,400</td>
</tr>
<tr>
<td>Vagina</td>
<td>700</td>
<td>500</td>
<td>400</td>
</tr>
<tr>
<td>Penis</td>
<td>1,000</td>
<td>400</td>
<td>300</td>
</tr>
<tr>
<td>Anus</td>
<td>4,700</td>
<td>4,500</td>
<td>4,200</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>11,700</td>
<td>7,400</td>
<td>7,000</td>
</tr>
<tr>
<td>TOTAL</td>
<td>33,400</td>
<td>25,900</td>
<td>22,600</td>
</tr>
</tbody>
</table>

HPV and Oral Cancer

- PubMed (10/31/12)
  - Human papillomavirus + oral
    501 published manuscripts
- PubMed (3/24/13)
  - Human papillomavirus + oral
    2075 published manuscripts
- PubMed (11/1/14)
  - Human papillomavirus + oral
    6188 published manuscripts
What does the data show?

- HPV is an *independent* risk factor for oral and oropharyngeal squamous carcinoma
  - Multiple studies; multiple institutions
  - ~30% prevalence rate of HPV detection in H&N cancer surgical specimens
  - Higher prevalence in oropharyngeal lesions (~35%) than laryngeal (~25%) or oral (<25%) lesions

HPV and Oral Cancer

- Dramatic increase in HPV-related oral cancers
  - 0.8 cases per 100,000 population (1988)
  - 2.6 cases per 100,000 population (2004)
- More common in men
- Thought to be due to increased incidence of oral sex
Which HPV is responsible?

- HPV-16
  - 86.7% of oropharyngeal lesions
  - 68.2% of oral lesions
  - 69.2% of laryngeal lesions

Is HPV-related H&N SCC different?

- Yes
  - Better prognosis
  - Better clinical outcome

Human Papillomavirus in HNSCC: Recognition of a Distinct Disease Type

Laura Vidal, MD, Maura L. Gillison, MD, PhD

Sex & Oropharyngeal Cancer

- Sexual behavior is associated with oropharyngeal carcinoma
- Related to lifetime # of sex partners
  - Vaginal sex and oral sex
- Open-mouth kissing
- HPV exposure precedes oropharyngeal cancer by at least 10 years

The Prevalence and Incidence of Oral Human Papillomavirus Infection Among Young Men and Women, Aged 18–30 Years

Robert K. L. Pickard, MS, MPH, EdM,* Weihong Xiao, MD,* Tatarik R. Benjam, MS,† Xin He, PhD,‡ and Maury L. Gillison, MD, PhD*

Sex Trans Dis 2012;39:559-66

Oral sexual behaviors associated with prevalent oral human papillomavirus infection


How big is the problem?
HPV Vaccines

- Bivalent (HPV 16 and 18) and quadravalent (HPV 16, 18, 6 and 11)
- Little benefit to previously infected individuals
- 49% of teenage girls in USA vaccinated in 2010

HPV Vaccines – 3 Injections

- Cervarix
  - Bivalent
  - Females 9-25
  - Cervical cancer (HPV 16, 18)

- Gardasil
  - Quadravalent
  - Females and males 9-26
  - Cervical cancer (HPV 16, 18)
  - Genital warts (HPV 6, 11)

FDA News Release

FDA approves Gardasil 9 for prevention of certain cancers caused by five additional types of HPV

For Immediate Release

December 10, 2014

The U.S. Food and Drug Administration today approved Gardasil 9 (human papillomavirus 9-valent vaccine). Recombinant for the prevention of certain diseases caused by nine types of human papillomavirus (HPV). Covering nine HPV types: five more HPV types than Gardasil previously approved by the FDA. Gardasil 9 has the potential to prevent approximately 90 percent of cervical, vulvar, vaginal and anal cancers.

Gardasil 9 is a vaccine approved for use in females ages 9 through 26 and males ages 9 through 15. It is approved for the prevention of cervical, vulvar, vaginal and anal cancers caused by HPV types 16, 18, 31, 33, 45, 52 and 58, and for the prevention of genital warts caused by HPV types 6 or 11. Gardasil 9 adds protection against five additional HPV types—31, 33, 45, 52 and 56—which cause approximately 20 percent of cervical cancers and are not covered by previously FDA-approved HPV vaccines.
Unanswered Questions

- Do we treat HPV-positive premalignant, i.e., dysplastic, oropharyngeal lesions differently?
- Do we treat HPV-positive malignant oropharyngeal lesions differently?
- Would some oropharyngeal cancers be prevented by HPV vaccination?
Questions With No Answers

- Is HPV transmitted by kissing? Deep kissing? How deep? How do you test this?
- If HPV is transmitted by kissing, are you “giving” someone oral cancer.
- Is there a risk of mother-child transmission?


Even More Questions With No Answers

- If a latent infection reappears, how does your spouse know it’s not a “new” infection?
- Who should be tested? Everybody?
- Is HPV positivity in an adolescent a marker for sexual activity?
- When do you recheck an HPV+ patient?
- How about the rest of the family?


Oral Cancer
New Oral Cancer Cases and Deaths – 2014

<table>
<thead>
<tr>
<th>Estimated Number* of New Cancer Cases and Deaths by Sex, US, 2014</th>
<th>Estimated New Cases</th>
<th>Estimated Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Both Sexes Male</td>
<td>Female</td>
</tr>
<tr>
<td>All Sites</td>
<td>405,930</td>
<td>193,220</td>
</tr>
<tr>
<td>Oral cavity &amp; oropharynx</td>
<td>30,400</td>
<td>10,500</td>
</tr>
<tr>
<td>Mouth</td>
<td>14,200</td>
<td>6,100</td>
</tr>
<tr>
<td>Nose</td>
<td>11,600</td>
<td>7,300</td>
</tr>
<tr>
<td>Other oral sites</td>
<td>16,700</td>
<td>9,400</td>
</tr>
</tbody>
</table>
Risk Factors
- Intrinsic
  - Nutrition
  - Anemia
  - Immunosuppression
  - Oncogenes

Risk Factors
- Extrinsic
  - Tobacco
  - Alcohol
  - Tobacco AND alcohol (40x risk)
  - Ultraviolet radiation
  - Microbes

Tobacco Advertising
- Increased graphic warnings for cigarettes scheduled for September 2012
- Congress told the images would be frightening and disturbing to smokers
- Died a “political death”
## Unhealthy Alcohol Use

<table>
<thead>
<tr>
<th>Category of Use</th>
<th>Prevalence</th>
<th>Definition and Features</th>
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<tbody>
<tr>
<td>Risky use</td>
<td>30%</td>
<td>&gt;65 years - &gt;7 drinks/week or &gt;3 drinks/occasion &lt;65 years - &gt;14 drinks/week or &gt;4 drinks/occasion</td>
</tr>
<tr>
<td>Problem drinking</td>
<td>Varies</td>
<td>Alcohol-related consequences, e.g., &quot;hangover&quot;</td>
</tr>
<tr>
<td>Alcohol abuse, harmful use</td>
<td>5%</td>
<td>Failure to fulfill major role obligations; use in hazardous situations; alcohol-related legal problems; social or interpersonal problems</td>
</tr>
<tr>
<td>Alcohol dependence, alcoholism</td>
<td>4%</td>
<td>Clinically significant impairment or distress, plus 3 or more of the following: tolerance, withdrawal, excessive time spent obtaining, using or recovering from use, drinking more or longer than intended, inability to control use, continued use despite problems</td>
</tr>
</tbody>
</table>

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## Ultraviolet Radiation

### Clinical Features

- 90% of cases
  - lower lip
  - ventral tongue
  - floor of mouth
- Most cases present for at least 1 year as an asymptomatic lesion
Clinical Features
- Leukoplakic (white)
- Endophytic (ulcerating)
- Exophytic (fungating)
- Erythroplakic (red)

Diagnostic Techniques
- Scalpel biopsy
- Punch biopsy

Therapeutic Modalities
Multidisciplinary Therapy

- Surgery
- Radiation therapy
- Combination therapy
- Periodic reassessment

Prognosis

- Depends on location and progression
- More anterior location
- No regional lymph node involvement
- No distant metastasis

Grading

- Assessment of biologic behavior based on microscopic features of pleomorphism, cellular maturation, keratin production, etc.
- Grade I – well differentiated
- Grade II – moderately well differentiated
- Grade III – moderately differentiated
- Grade IV – poorly differentiated
### Staging

- Assessment of survival based on a combination of factors:
  - tumor size (T)
  - regional lymph node involvement (N)
  - distant metastasis (M)
- TNM system

<table>
<thead>
<tr>
<th>Staging Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>not assessed</td>
</tr>
<tr>
<td>T0</td>
<td>no evidence of tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>carcinoma <em>in situ</em></td>
</tr>
<tr>
<td>T1</td>
<td>&lt;2 cm</td>
</tr>
<tr>
<td>T2</td>
<td>2-4 cm</td>
</tr>
<tr>
<td>T3</td>
<td>&gt;4 cm</td>
</tr>
<tr>
<td>T4</td>
<td>invading adjacent structures</td>
</tr>
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</table>

### TNM Staging

<table>
<thead>
<tr>
<th>Staging Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>not assessed</td>
</tr>
<tr>
<td>N0</td>
<td>no nodal involvement</td>
</tr>
<tr>
<td>N1</td>
<td>single, ipsilateral node, &lt;3 cm</td>
</tr>
<tr>
<td>N2</td>
<td>nodal metastasis, 3-6 cm</td>
</tr>
<tr>
<td>N2a</td>
<td>single, ipsilateral node, 3-6 cm</td>
</tr>
<tr>
<td>N2b</td>
<td>multiple ipsilateral nodes, &lt;6 cm</td>
</tr>
<tr>
<td>N2c</td>
<td>bilateral or contralateral nodes, &lt;6 cm</td>
</tr>
<tr>
<td>N3</td>
<td>nodal metastasis, &gt;6 cm</td>
</tr>
</tbody>
</table>
TNM Staging

- MX – not assessed
- M0 – no distant metastasis
- M1 – distant metastasis

TNM Staging

<table>
<thead>
<tr>
<th>TNM</th>
<th>STAGE</th>
<th>5 YEAR SURVIVAL</th>
</tr>
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<tbody>
<tr>
<td>T1N0M0</td>
<td>Stage I</td>
<td>85%</td>
</tr>
<tr>
<td>T2N0M0</td>
<td>Stage II</td>
<td>66%</td>
</tr>
<tr>
<td>T3N0M0</td>
<td>Stage III</td>
<td>41%</td>
</tr>
<tr>
<td>T1-3N1M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any T4</td>
<td>Stage IV</td>
<td>9%</td>
</tr>
<tr>
<td>Any N2-3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any M1</td>
<td></td>
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</tr>
</tbody>
</table>

Stage I: 85%
Stage II: 66%
Stage III: 41%
Stage IV: 9%
Stage IV: 85%
Stage IV: 66%
Stage IV: 41%
Stage IV: 9%